IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:
BUSH *et al.*
Appl. No. 10/643,226
Filed: August 19, 2003
For: **Method of Screening for Drugs Useful in Treating Alzheimer's Disease**

Confirmation No.: 3164
Art Unit: 1649
Examiner: Dutt, A.
Atty. Docket: 0609.4810002/TJS/LMB

Declaration of Kevin J. Barnham, Ph.D. Under 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

1. I, the undersigned, Kevin J. Barnham, Ph.D. declare and state that:

2. A recent copy of my Curriculum Vitae, accurately listing my scientific credentials and work experience, is attached hereto as Exhibit 1.

3. I have read and am familiar with the above-captioned patent application, including the specification, drawings, and currently pending claims. I have also read and am familiar with the amended claims that are being submitted concurrently with this Declaration.

4. I have read and am familiar with Dyrks, T., *et al.*, "Amyloidogenicity of βA4 and βA4-bearing Amyloid Protein Precursor Fragments by Metal-catalyzed Oxidation," *Journal of Biological Chemistry*, 267 (25): 18210-18217, 1992 (hereinafter "the Dyrks reference").

5. I have read and am familiar with the Office Action issued in the above-captioned patent application on May 9, 2006, in which the Examiner rejected claim 36 as being anticipated by the Dyrks reference, and in which

the Examiner rejected claim 37 as being obvious over the Dyrks reference.

6. I understand that the invention encompassed by the currently presented claims is a method for the identification of an agent to be used in the treatment of Alzheimer's disease (AD), wherein the agent is capable of inhibiting redox-reactive metal-mediated crosslinking of amyloid beta (Aβ) comprising (a) adding a redox-reactive metal to a first Aβ peptide sample; (b) allowing the first sample to incubate to allow Aβ crosslinking; (c) adding the redox-reactive metal to a second Aβ sample comprising a candidate pharmacological agent; (d) allowing the second sample to incubate for the same amount of time as the first sample; (e) removing an aliquot from each of the first and second samples; and (f) determining presence or absence of crosslinking in the first and second samples.

7. The Dyrks reference describes the aggregation properties of Aβ (referred to as βA4 in the Dyrks reference) and A4CT. (*See*, the Dyrks reference, page 18211, lines 16-22, left column.)

8. A4CT consists of the C-terminal 100 residues of amyloid protein precursor (APP) which includes the Aβ peptide.

9. The Dyrks reference describes that incubation of A4CT with hemoglobin and H_2O_2 causes aggregation of A4CT. (*See*, the Dyrks reference, page 18212, lines 38-41, right column.)

10. The Dyrks reference describes that the addition of amino acids, vitamin C and trolox inhibits hemoglobin- and H_2O_2-induced aggregation of A4CT, suggesting that the aggregation of A4CT is catalyzed by metal catalyzed oxidation. (*See*, the Dyrks reference, page 18213, lines 24-32, left column).

11. The Dyrks reference describes that hemoglobin and H_2O_2 cause aggregation of βA4, but does not describe the use of an agent to reduce or inhibit βA4 aggregation. (*See*, the Dyrks reference, page 18214, lines 7-11, right

column.)

12. Metal catalyzed oxidation defines a series of reactions where a biological substrate (*e.g.*, amino acids) reacts with oxygen.

13. The chemical nature of the biological substrate determines what types of metal catalyzed oxidation products are formed, as different amino acids react in different ways.

14. The Dyrks reference supports the proposition that metal catalyzed oxidation is dependent upon the chemical nature of the biological substrate, as additional amino acids were found to interfere with oxidation of A4CT catalyzed by bivalent metal ions. (*See*, the Dyrks reference, page 18212, lines 32-34, right column.)

15. Accordingly, the chemical nature of A4CT is different than that of Aβ because A4CT has an additional 58 amino acid residues, many of which are susceptible to metal catalyzed oxidation.

16. Thus, it is expected that A4CT and Aβ will give rise to differing arrays of oxidatively modified products if subjected to metal catalyzed oxidation.

17. Given the differing arrays of oxidatively modified products likely to be generated by metal catalyzed oxidation of A4CT and Aβ, it is likely that different oxidation modifications are responsible for the observed hemoglobin- and H_2O_2-induced aggregation of A4CT and Aβ in the Dyrks reference.

18. Due to the likelihood that different oxidation modifications are responsible, one would have no reasonable expectation to believe that the addition of the agents that inhibited hemoglobin- and H_2O_2-induced aggregation of A4CT would also inhibit hemoglobin- and H_2O_2-induced aggregation of Aβ.

19. Thus, the Dyrks reference does not describe the method of the present

claims which involves the addition of an agent capable of inhibiting redox-reactive metal-mediated crosslinking of Aβ, or create a reasonable expectation of success for the method of the present claims.

20. I hereby declare that all statements made on our own knowledge are true and that all statements made on information and belief are believed to be true; and further that theses statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the U.S. Code and may jeopardize the validity of the application or any patent issuing thereon.

4/10/06
Date

Kevin J. Barnham, Ph.D.

578784_1.DOC